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14. ABSTRACT
This project is to perform translational research tasks needed to prepare an intracortical visual prosthesis (ICVP) for testing in a human. No human trial testing of the prosthesis will occur under the funded work. Preparatory tasks include final maturation of the implantable hardware, pre FDA IDE testing of the ICVP in non-human primates, reliability and biocompatibility testing, development of a human testing protocol, development of a human volunteer selection and assessment protocol, preparation of an investigation device exemption application (IDE) to the FDA. Progress to-date has been somewhat hampered by delayed approval of the psychology testing protocols (human subjects), and the animal testing protocols (non-human primates), by the USARMYMC. However, all protocol approvals have now been obtained. This delay has also slowed the spending of funds for these areas within the first year. The work focused on technology maturation has been highly productive. Sample stimulator units have been subjected to brutal environmental testing with 100% survival. Larger numbers of stimulator units are in the process of being constructed to provide statistical power for the environmental testing. Following the human protocol acceptances, work has commenced at both IIT and Johns Hopkins for the development of the testing and assessment protocols. A graduate student from IIT has initiated work within the laboratory of Dr. Dagnelie at JHU. Analysis of interview data from the earlier Dobelle visual prosthesis recipients has already yielded valuable insight about the volunteer recruitment and participation process. Sixteen publications and presentations have resulted from the funded work, and several publications are in preparation. While the project is projected for a 1-year no-cost extension request, due to the slow start-up, it is anticipated that by the end of the project all parts of the SOW will be complete, with the ICVP ready for clinical testing in a human trial.

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INTRODUCTION

The objective of this project is to prepare for clinical feasibility testing of an intracortical visual prosthesis (ICVP) in humans. Our hypothesis is that an ICVP is technically and surgically feasible, has a sufficient likelihood of sensory benefit to warrant human testing, and that our ICVP team is at the point of readiness for proceeding towards a first human clinical trial. While the project will NOT support human testing, per se, it will accomplish all of the necessary steps to prepare the ICVP for testing in a human volunteer. The study uses a well-established project team lead by the Illinois Institute of Technology comprised of: Sigenics, Inc, MicroProbes for Life Science (MLS), University of Chicago (UC), Huntington Medical Research Institutes (HMRI), and Johns Hopkins University (JHU). The project work addresses a military-relevant health problem of compensating for vision loss because over 90% of those individuals with blindness, in the military and civilian population are not gainfully employed and often suffer from depression, social isolation, and a significantly-reduced quality of life.

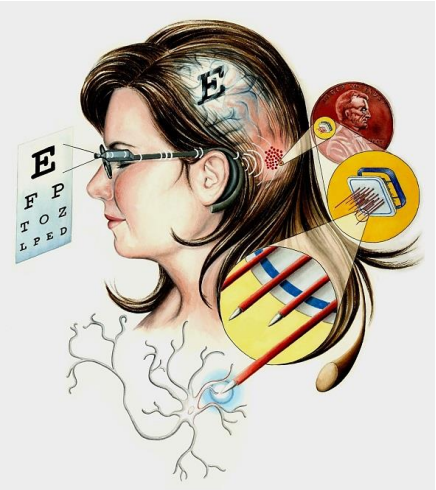

Figure 1 - Artist's concept drawing of the ICVP. A collection of miniature wireless stimulator modules (WFMA) implanted on the occipital lobe communicate artificial image information directly to the visual cortex. Electrode size is shown relative to a human hair.

This project is now completed. All of the project goals have been met, with a slight modification to the outcomes of SOW Task 6 (see below). The ICVP system is now ready for human clinical trial testing, and a clinical trial proposal has been submitted to the NIH for the testing of the ICVP in five human volunteers.

THE STATEMENT OF WORK (SOW)
(As presented in the proposal)

Our long-term hypothesis to be tested is that spatial-temporal electrical stimulation of the cortical visual system can provide usable visual sensation and restoration for those individuals with blindness. The objective of this proposed project is to make possible feasibility testing of an intracortical visual prosthesis (ICVP) in humans. While the proposed project will NOT support human testing, per se, it will accomplish all of the necessary steps to prepare the ICVP for testing in a human volunteer. The proposed work addresses a military-relevant health problem of compensating for vision loss because over 90% of those individuals with blindness, in the military and civilian population are not gainfully employed and often suffer from depression, social isolation, and a significantly-reduced quality of life. The potential contribution that the proposed study could make to addressing these issues is that by preparing the ICVP for clinical testing, a potentially ground-breaking alternative could become available to those with blindness.

For the past decade, Illinois Institute of Technology (IIT) has lead a team-based project, consisting of multiple institutions, to advance the ICVP - for which micro-sized wire electrodes provide electrical stimulation directly to the visual cortex. During this time, accomplishments have been achieved for development of electrode materials, electrode array fabrication, implantable wireless hardware design, implantable stimulator fabrication and stress testing, non-human primate psychophysics, normal human psychophysics, surgical feasibility assessment, and psychological assessment of potential and past vision prosthesis recipients. Our hypothesis is that an ICVP is technically and surgically feasible, has a sufficient likelihood of sensory benefit to warrant human testing, and that our ICVP team is at the point of readiness for proceeding towards a first human clinical trial.

The proposed study will use a well-established project team lead by Dr. Troyk of IIT. This team is comprised of six institutions: Illinois Institute of Technology, Sigenics, Inc, MicroProbes for Life Science (MLS), University of Chicago (UC), Huntington Medical Research Institutes (HMRI), and Johns Hopkins University (JHU). Each member of the team brings highly-targeted expertise to address the following six program components. In order to accomplish the ambitious long-term project goal, key steps must be taken to prepare our ICVP system for clinical testing. These comprise the SOW and are (the order of organizations indicates task responsibility):

1. Design evaluation and fabrication of large numbers of implantable electrode array/stimulator modules (WFMA modules) under GLP and GMP conditions with suitable documentation for satisfying regulatory submission needs, within sustainable commercial organizations.

2. Testing of, and prediction of long-term biocompatibility and survivability for, (WFMA modules) in animal and laboratory evaluations.

3. Design and testing of a real-time psychophysical assessment and testing system for evaluation of an ICVP recipient, and design and fabrication of a first-generation portable image processing system for converting electronic images into cortical stimulation neural coding patterns

4. Design and implementation of a volunteer recruitment and evaluation process that preserves subject protection, integrity, and maximizes project scientific significance.

5. Constitute a team structure within a clinical setting for preparation of surgical implantation and human subject care.

6. Preparation and submission of an FDA IDE application for a human trial.

COMPLETION OF SOW TASK 1

TASK 1. Design evaluation and fabrication of large numbers of implantable electrode array/stimulator modules (ICVP modules) under GLP and GMP conditions with suitable documentation for satisfying regulatory submission needs, within sustainable commercial organizations.

The IVCP hardware system is comprised of two key components: the implantable stimulator modules (WFMA), and the extracorporeal telemetry controller (TC). The WFMA is shown in Figure 2. Both of these have come to a mature design state during the grant project period.

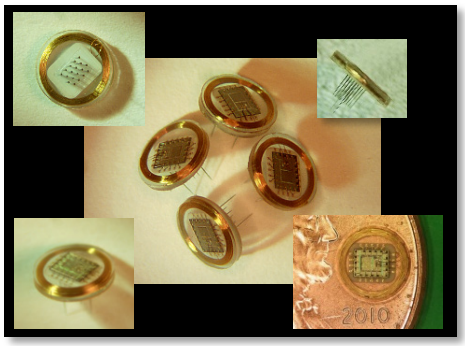

Figure 2 – Microphotographs of the WFMA implantable stimulator. Each of the 16 electrodes is controlled and stimulated by the wireless electronics. Each WFMA has a unique address. No tethering cables are necessary, reducing the physical stress placed upon the surrounding brain tissue.

The ISM is comprised of an application-specific-integrated circuit (ASIC), placed within an electrode array that contains a ceramic substrate which maintains the position of the electrodes while serving as an interconnection means between the ASIC and the electrodes, as shown in Figure 3. The electrodes are fabricated from pure iridium, and Activated Iridium Oxide Film (AIROF) is electrochemically grown on the electrode after all of the encapsulation processes have been completed. The AIROF film dramatically enhances the injectable charge capacity of the electrodes, and the growth of the film following the encapsulation processes is necessary because of the high curing temperatures for the silicone encapsulant (150C). The AIROF film cannot tolerate the elevated temperature without resulting in destruction. Therefore a unique functionality of the ASIC is that it can be commanded over WFMA wireless link to activate the electrodes after the assembly has been fully encapsulated.

Mature WFMA design using single 16-channel Application-Specific-Integrated-Circuit (ASIC) stimulator: As first reported in (Troyk, 2006, 2006), and shown in Figure 3, the WFMA is physically comprised of a ceramic substrate platform that maintains the lateral position of eighteen (16 + reference + counter) Parylene-insulated iridium microelectrodes, and provides electrical interconnection between a superstructure that contains an ASIC and microcoil, to form a fully-integrated autonomous wireless stimulator module. A group of WFMAs comprise the implanted portion of the ICVP System. The ASIC (chip) contains all required circuitry for power rectification and management, bidirectional communication, state-machine command processing, sixteen individual AIROF electrode drivers, and housekeeping support. The WFMA is powered by a 4.8 MHz inductive link that uses a gold-wire microcoil as reported in (Rush, 2011). It is easy to power and communicate with the WFMA with about 4cm of

separation between the extracorporeal telemetry controller (TC) and the WFMA. While space does not permit a

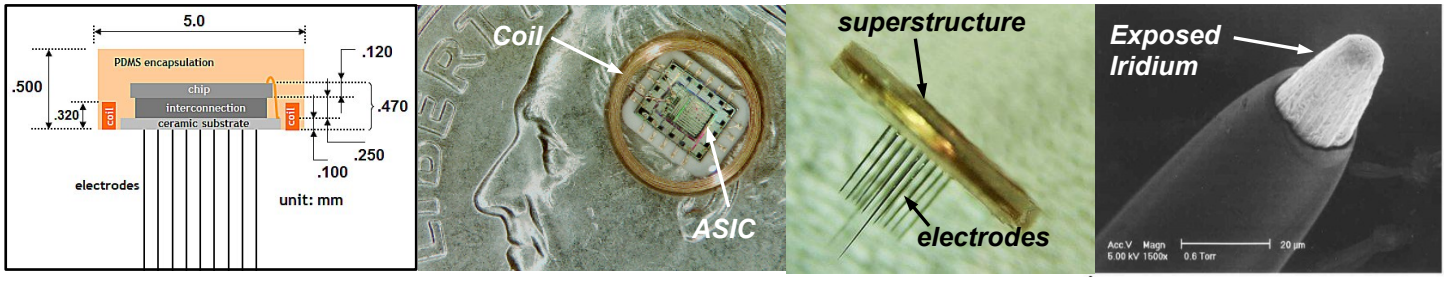

Figure 3. Details of the WFMA stimulator module. A: Sectional drawing of WFMA – for clarity not all drawing dimensions to scale. B: Top view of WFMA on US Dime. C: Side view of WFMA showing electrodes. D. SEM photograph of typical Goldilocks electrode; black is Parylene insulation, bright is iridium metal.

comprehensive description of the ASIC circuitry, a summary of the WFMA ASIC performance parameters are shown in Table B.1

Forward command telemetry to the WFMA is provided using FSK-modulation of the Class-E converter in the TC (Troyk, 2003), using the NeuroTalk interface (Troyk, 2006). Each WFMA has a unique address and up to 63 separate WFMAs (1008 electrodes) can be randomly addressed by one TC at a frame update rate of at least 60 Hz, (higher frame rate for less WFMA modules). Each electrode has an independently-controlled constant current cathodic-first electrode driver that uses potentiostatic control of the electrode voltage with respect to a non-current-carrying Pt-Ir reference electrode contained within the electrode cluster of the WFMA.

Table B.1 - WFMA Performance Parameters

Parameter	*Value*
Wireless Inductive Link	4.8MHz; FSK Modulation; 1.2Mbits/sec
Power Supply	5V regulated; 2.5nF on-chip Capacitance
Electrode Drivers	16 independent cathodic-first; charge balanced;AIROF biasing
Pulse Amplitude	0-64μA in 0.5 μA steps
Pulsewidth	0-450 μs in 30 μs steps
Outward Telemetry	145kHz; PWM; power supply and electrode voltage monitoring
ASIC Fabrication Technology	XFab CX08 die size: 1.8mm x 2.2mm

Electrode current flows between the micro-(working) electrode and a longer large-area counter electrode, using either compliance-supplied limited driving (Troyk, 2006), that unconditionally maintains the electrodes within the water window (± 0.6V wrt reference), or a 4.5V compliance supply range. The driving circuitry is configured for biasing the AIROF electrodes, to enhance, and optimize, the injectable charge capacity (Cogan, 2006). Outward telemetry permits extracorporeal monitoring of the WFMA power supply and each electrode voltage waveform. The TC unit contains an FSK-modulated, closed-loop Class-E converter (Troyk, 2013).

Table C.1.2 - GMP (QSR) Controlling Documents & related FDA GMP (QSR)		
Document	Description	FDA QSR 21CFR
DSOP	Design Control/Version/Revision	820.3
DMR	Device Master Record	820.40, 820.186
DHR	Device History Record	
SRS	System Requirements Specifications	
QOP	Quality of Protection	
RMS	Raw material Specification	820.5
SQF	Supplier Quality File	
QVS	Quality Vendor Specifications	
MLS-QMF	Quality Control Checklist	
MOPs	Manufacturer Operating Procedures	
ITSOP	Indentification and Traceability Controls	820.60, 820.65
	Production Process Controls	820.7
PPSOP	Receiving, in-process, finished device acceptance	820.8
	Equipment calibration verification	820.72
HSDSOP	Handling, Storage and Distribution Controls	820.140, 820.150, 820.160

Packaging of the WFMA uses silane-enhanced poly-dimethly-siloxane (PDMS) encapsulation. Overall dimensions of the superstructure are 5mm diameter by 0.5mm thick. In order to maximize the injectable charge capacity of the AIROF film, the electrode must be anodically-biased during the interpulse interval. The ICVP provides this bias, and automatically assures charge recovery and operation within the safe "water window" for the AIROF. In addition, the WFMA ASIC is capable of self-activation of the iridium electrodes over the wireless link to grow the AIROF (Hu, 2012) and is needed to avoid destruction of the AIROF during 150°C PDMS curing. The WFMA design is mature and ready for production fabrication at team-member MicroProbes for Life Science (MLS). Table C.1.2 shows the applicable documentary control that will be used for the WFMA manufacture at MLS. MLS is presently GMP-compliant All WFMAs will be delivered to IIT in sterile (STERRAD) packaging. MLS currently delivers electrodes used for human use and fabricated under GMP-compliance.

During the project period the assembly process for the WFMA has been matured and fabrication of numerous WFMAs has been demonstrated, and these have been used in animal and cadaver studies. Some of these units have

been tested in accelerated laboratory tests, as described in Progress for SOW TASK 2, below. The complete assembly process is shown in Figures 4 and 5. At the subassembly level, the ceramic substrate is populated with electrodes. Then the ASIC is attached to the substrate with subsequent wirebonding. The coil is directly wirebonded to the ASIC, and the ISM is encapsulated in a mold, to produce the ISM assembly shown in Figure 6. Variations upon the ISM, in which the coil is fully integrated with the electrodes and ASIC are shown in Figure 7, in which a pigtail coil is attached to the ASIC using a 2-wire cable. This pigtail ISM assembly allows for an extended range of magnetic operation, albeit with the addition of the tethering 2-wire cable.

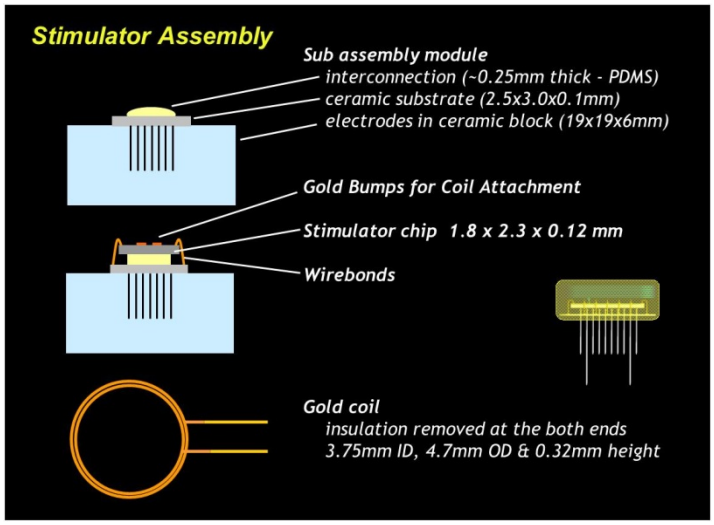

Figure 4 – Preliminary ISM assembly steps

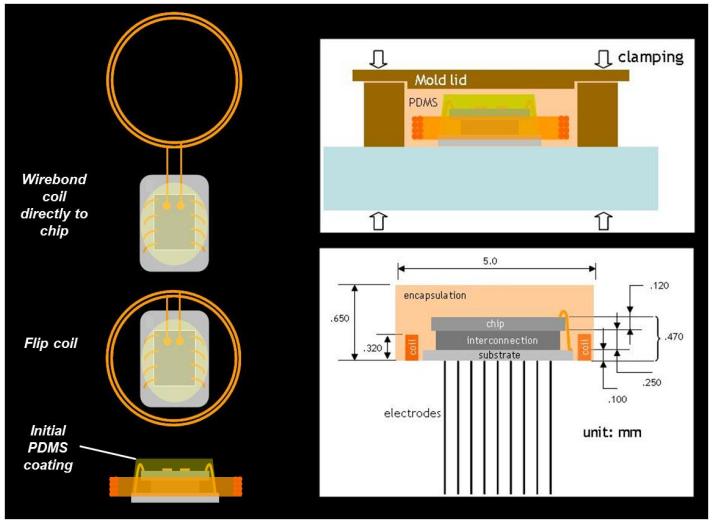

Figure 5 – Final ISM assembly steps

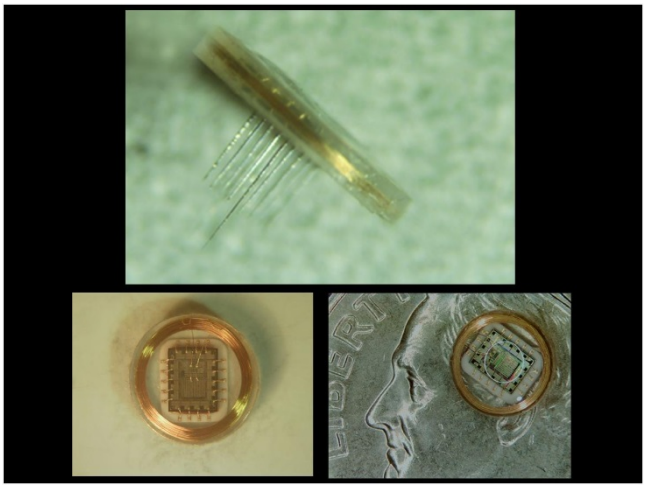

Figure 6 – Fully assembled ISM device

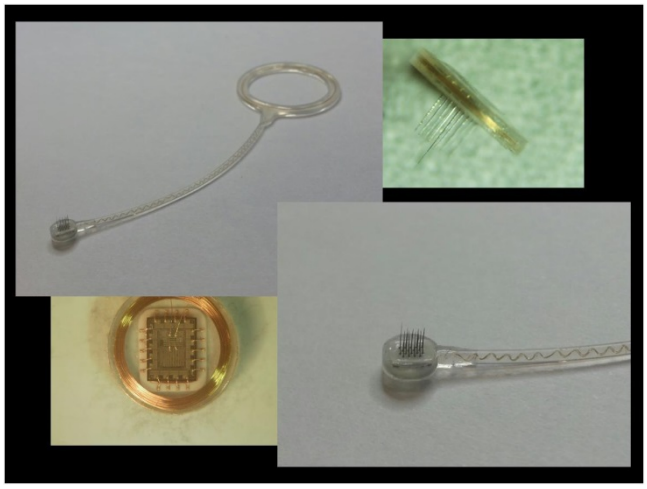

Figure 7 – Differing ISM models showing leaded vs non-leaded designs

The telemetry controller (TC) component, used for extracorporeal powering and control of the ICVP stimulator modules, has undergone design maturation within Sigenics. The TC reverse telemetry system, used to wireless monitor the critical system operational parameters (power supply, electrode polarization potentials), was completely redesigned in Y2.

In summary, all goals for SOW Task 1 have been accomplished.

COMPLETION OF SOW TASK 2

Task 2. Testing of, and prediction of long-term biocompatibility and survivability for, (WFMA modules) in animal and laboratory evaluations

Although conventional hermetic packaging is the most commonly used packaging for implantable devices, the small size of the WMFA precludes its use. Therefore, we have tested the capability of our PDMS packaging for chronic implantation using highly accelerated (brutal) temperature-humidity-bias (THB) laboratory tests. During THB, the WFMA devices have survived continuous electrical operation in an autoclave-type environment (100%RH, 20psi, 121°C – and direct immersion in saline liquid within the THB chamber, (Suh, Troyk, Hu, 2014), for over 250 days (currently still under test with no failures). The robust survival of the WFMAs in THB prevents calculating an activation energy needed to estimate the acceleration rate, above body temperature, provided by the THB testing. The commonly used "2x factor for each 10°C," results in an estimated acceleration factor to be 337x, or over 200 years. Even allowing for notable uncertainty in the 337x factor, each month of testing in the THB chamber represents years of operation at implanted body conditions. This demonstrates the robustness of the WFMA packaging for use in the early feasibility study trial.

To test MRI compatibility of the WFMA, we placed two WFMA devices within a 1.5T scan typical of that which a patient would receive during a head scan. The devices were placed at 90° relative orientation on a grapefruit. No visible distortion was seen in the MRI scan. Following the scan, the devices were verified to be electrically identical to their performance before the scan. They are also do not affect, nor are damaged by CT scanning. To demonstrate compatibility with STERRAD sterilization, multiple WFMAs were subjected to repeated sterilization cycles prior to implantation in Lewis rats and in two Macaque (below). No device failures or malfunctions resulted. This suggests that implanted WFMAs will not interfere with CT/MRI imaging and they survive both imaging and sterilization.

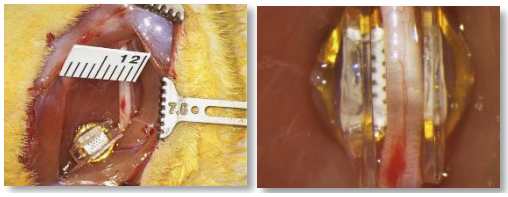

Figure 8. WFMA devices mounted to silicone cuff used in Rat sciatic nerve implantations at UTD. Left: next to nerve, Right: implanted

To demonstrate the WFMA, in-vivo, for stimulating neural tissue, two different experimental procedures were performed (not all were funded by this project, but are highly relevant to the accomplishment of the project goals and are presented here):

1. Two WFMAs were used in two acute, and two chronic implantations in adult Lewis rats with the WFMA contained within a silicone cuff (Figure 8), and placed upon the sciatic nerve (Troyk, et. al, 2015, Bredeson et. al 2015). The WFMAs were used to produce movements of the rat digits. Continued operation of the chronically-implanted WFMA has been confirmed after 16 months (rats died of natural causes unrelated to the WFMA implantations) with no evidence of electrical malfunction, and stable neural thresholds throughout. Table B.2 shows the converging stability of the neural interface formed by the WFMA as evidenced in the measurement of stimulation thresholds vs. time. This shows long-term in-vivo WFMA stimulation threshold stability.

WFMA Stability of Average µA Thresholds for Peripheral Nerve Implanted WFMAs (32 electrodes)				
Days Implanted			*% Δ per time period*	
Day 1	*Day 72*	*Day 142*	*% Δ D1-D72*	*% Δ D72-D142*
8.4	12.1	13.6	40%	12%

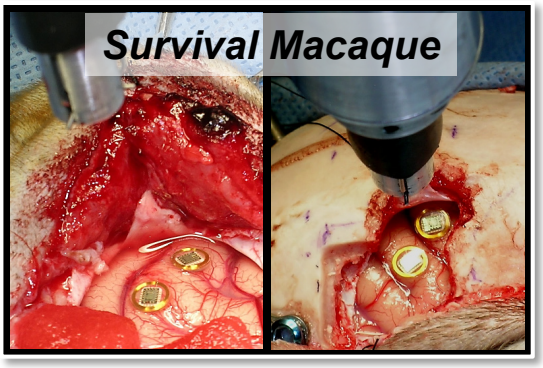

Figure 9. – WFMAs implanted in two macaques.

2. Our UC team neurosurgeons implanted two WFMAs in two Macaque (motor cortex – survival). The purpose of these implanted WFMA tests was to confirm the feasibility of cortical implantation and chronic use of the WFMA. Figure 9 shows the WFMAs implanted within the animals' brains immediately following insertion using our custom-designed rapid insertion tool. We measured the electrical functionality of the WFMAs and electrode voltage waveforms during stimulation, via reverse telemetry at 14 and 43 days (experiment on-going), showing that both the WFMAs and the electrode/tissue interfaces are stable as evidenced by minor changes in electrode access resistance and polarization. Although the protocols for these animals were not planned as controlled non-human primate motor experiments in which the animals were head-constrained, we also observed motor movements

Table B.3			
WFMA Stability for Macaque Cortical Implants Averages for 32 electrodes (2 WFMAs)			
Electrode Parameter	Days Implanted		
	in-vitro	Day 16	Day 43
Access Resistance (kΩ)	12.6	61.7	52.4
Polarization (V)	0.92	1.25	0.99

of the face, hand, and arm (anesthetized and awake, unrestrained), during stimulation of the motor cortex by the WFMAs. This demonstrates the surgical implantation of WFMAs in non-human primate cortex and stability of the electrode interfaces. This demonstrates our cortical surgical methods for the WFMA.

We performed mock surgeries on human cadaver to demonstrate the feasibility of implanting a group of WFMAs in humans. Our UC team neurosurgeons implanted nine WFMAs in a human cadaver during a mock surgery (Figure 10). In this procedure, we mimicked the steps that we plan to take for implanting the first human subject in our UH3 project phase. The entire procedure, starting with scalp opening, was accomplished in 45 minutes; the implantation of the nine WFMAs, using our high-speed insertion tool took under 15 minutes. The WFMAs were easily inserted by hand-holding of the tool, although for the actual clinical trial we will use more sophisticated means to position the tool above the brain. The advantage of the modular aspect of the WFMA stimulator can be seen in Figure B.9 in which the WFMAs were placed on and along gyri, accommodating the natural topology of the brain, and the WFMAs were selectively close together, or further apart. Following the insertion procedure, the WFMAs were removed, revealing no visible damage to the WFMA electrodes, from the insertion event, as shown in Figure 10. This demonstrates the feasibility of surgical implantion of multiple WFMAs in humans.

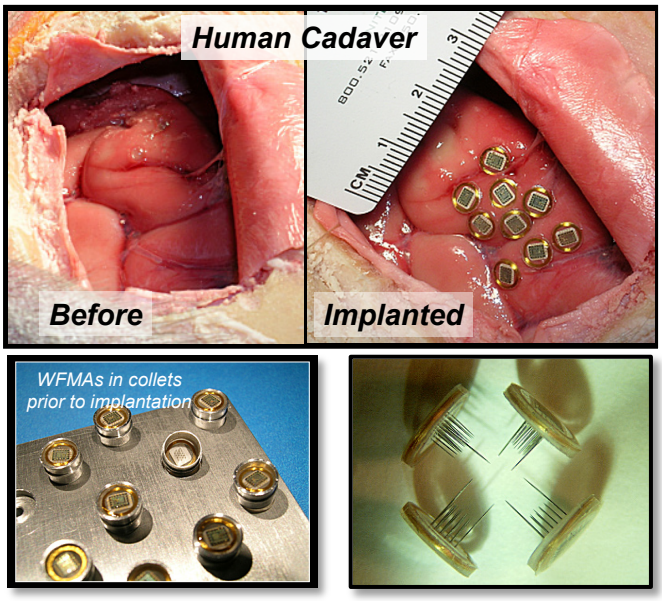

Figure 10. – WFMAs implanted in cadaver occipital lobe (top). WFMAs within inserter tool collets (bottom left).
WFMAs after removal from cadaver showing no electrode damage (bottom right).

We matured the design of, fabricated, and tested a WFMA rapid insertion tool for use in surgeries. To avoid damage to cortical tissue during implantation of WFMA devices, we utilize the high-speed insertion techniques as described by (Rousche, 1992; and McCreery, 2001). To propel the WFMAs into the brain at ~1m/sec, we have developed an electric high-speed insertion tool that uses a voice-coil motor (Bredeson and Troyk, 2014) to drive a plunger that inserts the WFMA into the brain (Figure 11). Directly handling of the WFMA devices is not possible because catastrophic damage to the electrodes would be certain; without a tethering cable there is no "handle" to hold the WFMA. In our tool design, the WFMA devices are preloaded into metal collets at the time of manufacture which then surround the WFMA and protect the electrodes from physical damage. The collects are automatically loaded into the tip of the inserter tool by downward pressure on the collet. Once loaded with the sterile collect containing the sterile WFMA, the tool is placed about 0.5mm above the brain surface and the motor is activated with an 8msec 6A pulse, followed by an equal amplitude reversing pulse, after which the motor is statically held in reverse position. The collet is then ejected and the tool is ready for loading of another collet/WFMA. The precise control offered by the voice-coil motor minimizes insertion pressure on the brain. We have used this tool to implant WFMAs in both Macaque and human cadaver. The ICVP insertion tool is a critical surgical accessory for quickly implanting many WFMAs.

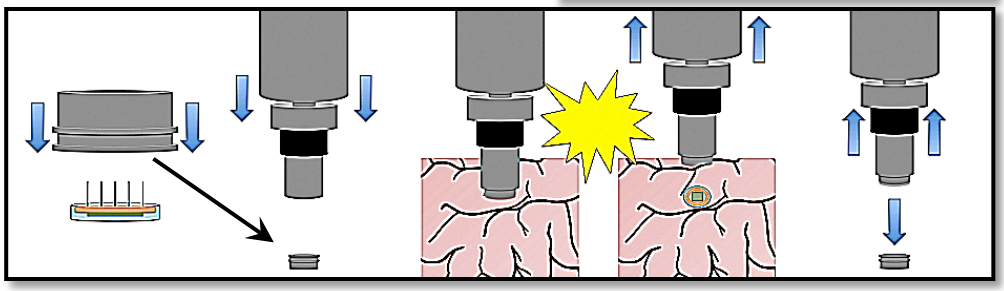

Figure 11. Depiction of the IIT High-Speed Insertion Tool. Left – Right: WFMA is loaded into collet; collect is loaded into tool; tool is positioned above the brain; high-speed insertion of WFMA; collect is ejected from the tool and ready for another WFMA insertion. (Above): Actual tool w/collet shown next to cm scale.

In summary, our testing of the WFMA modules and surgical methods during the project period have dramatically raised our confidence in the WFMA packaging method, and our expectation for implanted lifetimes that will most likely exceed the practical length of a first clinical trial. In the pre-clinical phase of our clinical trial NIH project, we will perform large animal GLP testing, and ISO10993 tests.

COMPLETION OF SOW TASK 3

Task 3. Design and testing of a real-time psychophysical assessment and testing system for evaluation of an ICVP recipient, and design and fabrication of a first-generation portable image processing system for converting electronic images into cortical stimulation neural coding patterns.

For this task, work has progressed at IIT, in combination with JHU. Under supervision of subcontract PI Gislin Dagnelie, PhD, Sr. Systems Manager Liancheng Yang and IIT graduate student Gayatri Kaskhedikar have developed phosphene mapping procedures allowing efficient and accurate creation of the spatial representation of each electrode's phosphene in visual space, and conversely of spatial coordinates onto the implanted electrodes.

In accordance with the Statement of Work for this subaward, most of the effort in the past year has been devoted to improving mapping methods and phosphene simulations, in preparation for use of these methods in future blind implantees. The development of phosphene dynamic range procedures and phosphene-based image transformation also received considerable attention, and software procedures for all 3 aspects of the project were developed in preparation for simulation tests in sighted subjects, carried out under separate funding (r01 EY021220, PI: Gislin Dagnelie, Ph.D.). Graduate student Gayatri Kaskhedikar spent several extended periods of time in the laboratory of her JHU advisor, Gislin Dagnelie, PhD, where in addition to her advisor she received assistance by Sr. Systems Manager Liancheng Yang and JHU undergraduate student Thomas Boucher.

In Ms. Kaskhedikar's study, the methods for assessing phosphene mapping in cortical prosthesis recipients was accomplished by providing sighted individuals with simulated phosphenes. The functional adequacy of the map was ascertained from the subject's ability to perform visually-guided tasks when provided with the simulated prosthetic vision obtained by the overlaying the phosphene map on the visual imagery.

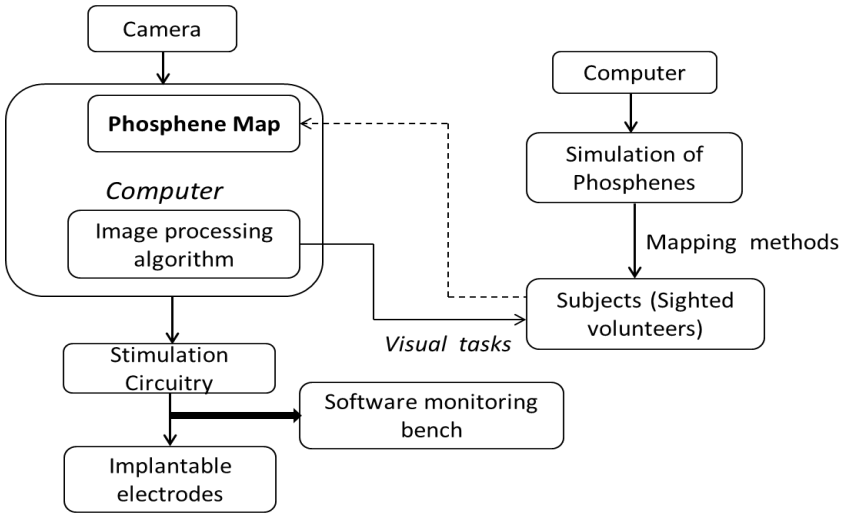

Figure 12. Design of the experiments.

Ms. Kaskhedikar and Mr. Boucher worked out the calibration procedures for the laboratory data collection system consisting of: 1) a high-resolution display used to present simulated phosphenes to sighted individuals; 2) an infrared pupil tracking system capable of recording eye movements at 60 frames/s; and 3) a touchscreen allowing the viewer to indicate the perceived location of presented phosphenes. Three separate mapping methods were designed, implemented, and validated:

- A touchscreen-based absolute mapping method, in which the subject moves the finger across the touchscreen from the center to the perceived location of a phosphene, without breaking fixation from a central window verified by the eyetracker
- An eye movement method, in which the subject makes a saccadic eye movement to the remembered location of a briefly presented phosphene

- A relative mapping method, in which two phosphenes are presented in sequence, and the subject traces a line on the touchscreen representing the perceived direction of the 2nd phosphene relative to the 1st one.

Ms. Kaskhedikar worked out an analytical approach to combining the phosphene location information obtained from these 3 methods, taking into account the relative variability of each.

This mission-critical component of Ms. Kaskhedikar 's work has been the development and testing of Cortical Mapping Techniques. The distribution of phosphenes across the visual field cannot be predicted from the location of electrodes in the occipital cortex (Schmidt et al, 1996), due to differences in the exposed portion of V1 (Horton and Hoyt, 1991) and the multiple secondary visual projections whose topography differs between individuals (Shipp et al., 1995). To use intracortical electrodes for the presentation of phosphene imagery, a map linking each electrode to the location of the corresponding phosphene needs to be constructed. This process is complicated by the fact that eye movements cause a perceived shift in phosphene location, since a point on the retina, and thus on the visual cortex, now corresponds to a new location in the scene. This leads to considerable variability in the phosphene map; a combination of absolute – i.e., locating each phosphene in the field – and relative – locating phosphenes relative to each other – mapping methods is needed.

Although several other groups have designed methods for phosphene mapping (Stronks 2011) none have come up with integrated absolute and relative methods that include gaze control. With our approach overall absolute errors of up to 15% may remain, but relative positions within phosphene clusters are close to veridical; combining absolute and relative mapping data produced a map in which angular distortions are 0.016°±7.0°; we expect to obtain similar accuracies in ICVP recipients. In her most recent work, Ms. Kaskhedikar has convincingly demonstrated that 64-128 phosphene-like dots, randomly distributed across the central 30° of one hemifield, allow sighted subjects to count objects and perform eye-hand coordination and virtual wayfinding tasks, despite remaining mapping distortions (Kaskhedikar 2016). We have a mature integrated hardware/software mapping and test environment in Dr. Dagnelie's lab (that will be transferred to the Chicago Lighthouse), and efficient procedures at our disposal, with the evidence that usable vision with 64-128 phosphenes is possible.

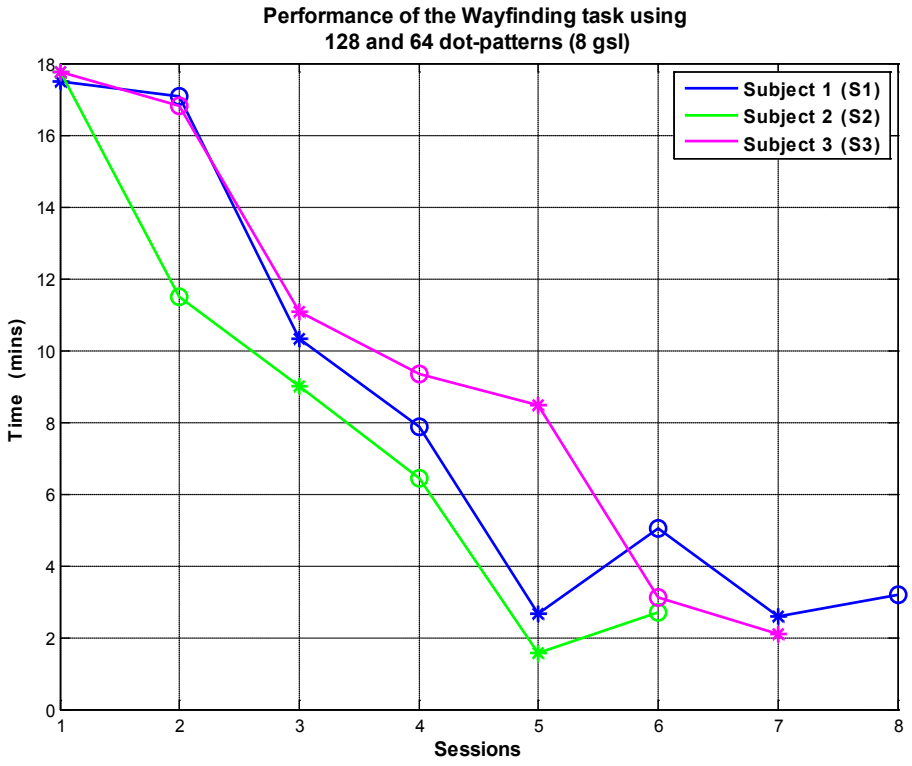

Figure 13. Plot of the average time (mins) to advance through 10 rooms of virtual maze in each session. Subjects used 128 dot-pattern (indicated by *) and 64 dot-pattern (indicated by o) alternately in the sessions.

In addition to the completion of phosphene mapping work, we have devised a rapid thresholding and dynamic range verification method, as well as an image transformation method for the presentation of common objects and space layout imagery through a phosphene "mask" obtained with the mapping methods described above. In the past year, we have

designed quality metrics for the recognition of phosphene-based object recognition and wayfinding using these images. These metrics have been evaluated in sighted subjects as part of Ms, Kaskhedikar's work at Hopkins.

We have also examined the ability of future ICVP recipients to perceive phosphene-based images and use the perceptions as part of visually guided tasks. Sighted individuals presented with simulated intracortical prosthetic vision (sICV) were assessed for their performance of tasks involving object recognition, eye-hand coordination and wayfinding. The sICV was a pattern of 128 or 64 dots adjusted to each subject's prior mapping estimations of the dot positions. Subjects were fitted with a head mounted display to present the sICV under gaze-locked conditions. Dot intensities were quantized to 4 or 8 grayscale levels (gsl). In the object recognition task, they counted 4 to 12 white squares in an irregular checkerboard; in the eye-hand coordination task they placed black checkers on these white squares. In the wayfinding task, they advanced through 10 rooms of 5 different virtual mazes using a game controller. The preliminary results showed that task performance improved across sessions and learning was observed both within and across sessions. The average maze completion time in 8 gsl which was not significantly different from 4 gsl, decreased over time across sessions (Fig.13). In the checkerboard tests, the average counting time decreased across sessions: 57.2±15.0 s to 28.9±8.2 s (S1), 78.2±20.1 to 40.2±10.3 (S2), 65.2±21.6 to 34.6±12.4 (S3). The percentage of correctly placed checkers decreased with increasing number of white fields on the board. These results indicate that for a phosphene count of 128, or perhaps 64, in an ICVP may allow the recipients to perform visually guided tasks and with training they may be able to improve their performance.

When Ms. Kaskhedikar was not at JHU, she developed a functional portable image processing system that an implanted volunteer can take home during the clinical trial (Figure 14).

In summary, the development of a testing system for mapping and evaluation of an implanted volunteer is mature and is of crucial importance to the planned clinical trial. Similarly, availability of a portable system that the volunteer can take home, out of the laboratory, is, beyond doubt, one of the most important requirements for volunteers (as determined by our work on Task 4). Both of these essential system components are ready for deployment in the clinical trial. All of the goals of Task 3 have been accomplished.

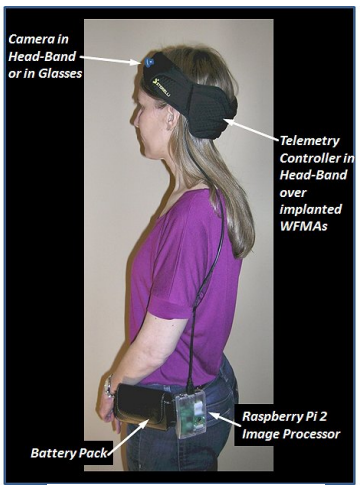

Figure 14.
Example of portable ICVP

COMPLETION OF SOW TASK 4

4. Design and implementation of a volunteer recruitment and evaluation process that preserves subject protection, integrity, and maximizes project scientific significance.

Understanding the psychological needs of potential volunteers is crucial to a successful clinical trial. Unless the volunteer is an authentic member of the research team, the likelihood of maximizing knowledge obtained from the trial is substantially reduced. Integration of the psychology component with the technical and medical components of our team is substantial. Students in Dr. Troyk's lab, who are pursuing the technology development, communicate regularly with students from Dr. Lane's lab who are involved with the development of the volunteer selection and evaluation protocols.

During this project, the psychology team completed the individual interviews of the Dobelle recipients. The research team traveled to the recipients' homes, had the interviews transcribed and engaged in in-depth analysis of the data.

A systematic analysis of the transcribed data was conducted. The videotape and audiotape files of the fourteen participants were professionally transcribed verbatim and a digital file was created. After the transcriptions were complete a second person checked the translations and made minor suggestions to improve their accuracy. We reviewed the transcripts for accuracy, which established the official record for analysis. The two co-investigators and research assistant independently reviewed the transcripts and "open-coded" the narrative. We compared the results and reached agreement on a coding scheme to be used for axial coding. The narrative was then re-analyzed and coded so that each portion of the text was coded on at least one axis.

Once axial coding was completed, we reviewed each theme to determine whether it was justified or could be captured under a different theme. After the axes were agreed upon, we met with the principal investigator of the research team who reviewed the data and assisted in the organization and interpretation of the results. This process was used to develop broader themes; a hierarchical structure emerged from the themes that were agreed upon by all investigators.

The manuscript describing the interviewing of the Dobelle recipients has been completed and is ready for submission.

The psychology team also recruited, screened and conducted three focus groups with individuals who are blind at the Chicago Lighthouse for the Blind. A total of 18 individuals participated in one of three focus groups over a period of two months. The focus groups lasted for two hours each and were audio and videotaped. The audio and video files have been transcribed. The final focus group with an additional 6 participants will be conducted in the upcoming year.

The psychology team has also conducted in-depth research on the prior recruitment and screening protocols, as used in the Dobelle study. The co-investigator of the psychology team contacted Dr. Beth Seelig, psychiatrist who screened the participants for an earlier version of the Dobelle implant.

User-Population Needs: Blindness Prevalence: Published figures for prevalence of blindness suffer from lack of consistency and non-uniform definitions of blindness. According to the Centers for Disease Control (CDC) and the World Health Organization (WHO) the classification of blindness includes (1, 2):

- •Legal blindness in the US means visual acuity of 20/200 or worse with the best possible correction, or a visual field of 20 degrees or less.
- •Blindness according to the WHO standard is defined as a visual acuity worse than 20/400 with the best possible correction, or a visual field of 10 degrees or less

Data collected from the National Health Interview Survey on Disability (1994-95) indicate that approximately 1.3 million persons reported legal blindness. Lighthouse International, the American Foundation for the Blind (2004) estimated that 10% of legally blind individuals have "light perception or less" representing an estimated 130,000 individuals.

The significance of our proposed ICVP system, from the standpoint of a future clinical deployment goes beyond the simple prevalence of blindness, no matter how one defines it. The estimated economic cost to society of those with blindness is staggering. The estimated annual cost of blindness to the federal government alone is $4 billion/year. Our proposed work addresses both health and quality-of-life issues because, without some compensatory strategy for vision loss, over two thirds of individuals with blindness are not gainfully employed (U.S. Department of Disability Statistics), experience higher rates of depression (Horowitz, *et al*, 2005), social isolation, and experience a reduced quality of life (WHO, 2014).

Table D.1 Studies by ICVP Team of Individuals with Blindness - Potential and Previous Visual Prosthesis Recipients

Study	*Participants*	*Description*	*Reference*
Chicago Focus Groups	52 people in 9 focus groups	Interviews about motivation, sensory substitution expectations, perceived risks and benefits	(Lane et al 2015, 2012, 2011; Troyk, 2009)
Optic Nerve Prosthesis	2 people who received an optic nerve prosthesis in Brussels, Belgium	Interviewed recipients about experiences with the prosthesis, motivation, benefits, disadvantages	(Lane, w/Troyk, 9/2010, et al, 2014)
TATRC Funded Focus Groups	32 people in 5 focus groups included US Veterans	Interviewed about motivation, sensory substitution expectations, perceived risks and benefits	In preparation
Dobelle Subject Alpha	First participant implanted by Dobelle in 1983	Conducted in-depth interview of participants to learn of experiences, motivations, visual percepts, risks and functional benefits	(Lane et al, 2015)
Dobelle participants	13/16 participants implanted by Dobelle in Lisbon, Portugal	Conducted in-depth interview of participants (world-wide) to learn about experiences, motivations, visual percepts, risks and functional benefits	(Lane et al, 2015, 9/2014, 5/2013, 5/2012, 9/2012; Dagnelie 10/2013)

In the 48 years since Giles Brindley published his first paper demonstrating that it was possible to produce sensations by electrically stimulating the visual cortex of a human (Brindley, 1968), no investigations had been conducted with the goal of understanding the psychology of the individual, until 2009, when Dr. Lane and other members from our team asked the questions: "What have been the experiences of the blind participants who received an implantable brain-based vision prosthesis?" and, "What do individuals with blindness think about an implantable vision prosthesis?" Since 2009, we have conducted five types of investigations (See Table D.1) to ask these questions and understand the psychology of the individual with blindness.

The current recruitment and screening protocols were developed based on the knowledge learned from our previous studies focused on the end-users of the ICVP. We have determined the significance of the following user needs-based factors:

1. Motivation. After interviewing prospective participants and individuals who had been previously implanted with a vision prosthesis in seven countries on four continents, altruism emerged as the appropriate, and perhaps expected, motivation for participating in a clinical trial, followed by a desire for a sense of adventure (Seelig & Dobelle, 2001; Seelig & Rosof, 2001) A desire to have one's vision restored also emerged as a strong motivator for participating. We learned that participants who were motivated by a strong desire to have their vision restored, coupled with unrealistic expectations and other signs of maladjustment, often experienced disappointment, anger and resentment. Therefore, motivation for vision restoration must be carefully assessed in combination with the participants' expectation for the vision prosthesis and adjustment to blindness. The importance of this for the proposed work is that: **The ICVP team has an understanding of what motivates an individual who is blind to participate in an experimental trial with no guarantee that their vision will be restored.**

2. Psychosocial Development and Ideal Participant Characteristics. The consensus was that middle-aged individuals, well-adjusted to blindness, available to meet the demands of the trial, ability to communicate clearly to investigators, who have a good social support system consisting of family and friends, and with an "easygoing personality" would be ideal. In terms of age, the belief is that younger adults will likely benefit from a future generation of vision prosthesis and it would therefore be unwise to implant an individual now and potentially prevent the younger adult's chance of a "better" implant in the future. The consensus was also that senior adults (above age 65) are more likely to have complicating medical conditions. The significance of this for our proposed project is: **Participants in each of our investigations were asked to identify preferred characteristics of participants for a vision prosthesis clinical trial.**

3. Adjustment to vision loss, depression, anxiety, and personality traits. It is important to identify an individual who is well adjusted to blindness but also has the personality characteristics to cope with stressors as they occur. The Acceptance and Self Worth Adjustment Scale (AS-WAS) is a 19-item adjustment scale that was developed by Tabrett and Latham (Tabrett, 2010) from the Nottingham Adjustment Scale (NAS) (Dodds, 1991) that was developed by Dodds. The authors of the scale recommend use of a depression and anxiety scale in conjunction with the AS-WAS when measuring adjustment and the underlying factors that contribute to level of adjustment. Tabrett and Latham found that individuals who were high in neuroticism and low in conscientiousness, as measured by the NEO-FFI, experienced difficulties with adjusting to vision loss (Tabrett, 2012). *One theme emerged from all interviews:* ***If participants regain visual percepts (even with minimal visual function) and the percepts are later lost, the individual will experience a re-adjustment phase similar to when they originally lost their sight.***

4. Vision restoration expectations and Hope. Participants in experimental vision trials (e.g. the Dobelle studies) who had an unrealistic expectation of vision restoration experienced devastating consequences that included feelings of anger, shame and resentment. We have also learned that when the participants expectations are appropriate, they have a positive overall experience, feel hopeful and experience an improved overall quality of life, even if the implant does not result in usable visual percepts. In contrast to realistic expectations are feelings of hope, participants' hope and realistic expectations must be balanced carefully. In trying to ensure that individuals are sufficiently informed, reality can be over-stressed which can destroy the candidates' hopes and can undermine their motives to behave altruistically. **It is crucial that in the ICVP study's Informed Consent Form the participants' expectations are matched with the expectations of the investigators and the capability of the device.**

5. Restoration of Function and Quality of Life (QOL). From the perspective of an individual who is blind, any visual percepts that restore function are beneficial. Individuals often focus on safety and independence as primary benefits of improved function. However, we have heard from people with vision prostheses implanted by Dobelle that their **quality of life improved for reasons unrelated to function.** One individual interviewed relayed feelings of joy when describing: "I could always tell when I was looking at an oak tree because there would be a lot of them (phosphenes) and they would be the most brilliant colors". While this self-report of previous visual-prosthesis induced perception cannot be verified, the statement by the recipient does illustrate the complexities of assessing potential ICVP effects upon quality of life.

The Functional Low-Vision Observer Rated Assessment (**FLORA**), an instrument developed with Argus II recipients to measure functional vision for prosthetic vision users, was recently published. It includes a semi-structured interview portion as well as a more formal assessment of an individual's ability to accomplish activities of daily living and utilize orientation and mobility skills. The FLORA is the only appropriate and available measure to assess the changes in the physical or functional quality of life domain that is specifically designed for a prosthetic vision user. The FLORA's reliance on the rater's qualitative analysis of individual self-report is not sufficient as a measure of quality of life. In order to obtain a quantitative measure of an individual that includes all components of an individual's quality of life and measure possible changes to quality of life, **we will supplement the FLORA by adding a single global item with an eleven-point interval scale.** This will allow the recipient to measure quality of life in a way that is inclusive of all quality of life dimensions as they relate to the individual recipients' lives. As explained in section UH.4.5 of the Clinical Protocol, we will also use two calibrated self-report instruments and two functional assessments specifically developed for individuals with extremely limited vision.

6. Role of participant and psychology. We have learned that the role of the participant and the role of the psychologist in the clinical trial are important from the perspective of the individual. Participants motivated by altruism and an adventurous spirit derive enjoyment from having opportunities to share their experiences and observations with investigators and other members of the project. Participants are likely to form a bond with members of the team and with other participants in the project. Participants in previous studies who maintained contact with the psychologist who was involved in the recruitment and screening process and who also maintained involvement with the project participants throughout the clinical trial, found it beneficial to have someone whom they trusted, and could process complex information with, and, in some cases, ask to be an advocate. The information necessary to make initial and ongoing decisions about vision prostheses is highly complex and the potential for misunderstanding is high (Nitsch *et al,* 2014). *It became clear that psychological monitoring of the candidate pool and implanted participants is important for the protection of the human participants.*

Based upon all of this work, we have developed the Subject Selection Criteria as stated in the SOW Task 4:

Blindess State and Psychological ICVP Participation Inclusion/Exclusion Criteria			
Criteria for ICVP Subjects	***Category***		
	Ideal	***Acceptable***	***Ineligible***
Vision loss	Report no light	Report light perception in one eye	Report light perception
Adjustment to Blindness	Well adjusted to blindness (AS-WAS)	Moderately adjusted to blindness (AS-WAS)	Poor adjustment to blindness or lost sight within the past year (AS-WAS)
Expectations of ICVP	No expectations for vision, not even visual percepts	Hopeful to see visual percepts	Expect restoration of pre-blindness vision
Willingness to meet demands of study	Able to meet all demands of the study	Able to meet the scheduling demands and physical demands but requires assistance with transportation	Unable to meet one or more of the demands of the study, with the exception of transportation
Motivation	Altruism	Restoration of artificial vision, participate in pioneering science	Restoration of pre-blindness vision
Social support	Access to daily support from spouse/significant other, family and friends	Access to support from spouse/significant other, family and friends on an as needed basis and regular support least once per week	No regular access to social support-social isolation
Mental Health History*	No history of mental illness	History of mental health issues that were remediated with treatment or regarded as minor (e.g. adjustment disorder, caffeine dependence)	History of chronic or severe mental illness (e.g. personality disorder, bipolar disorder, schizophrenia)
Substance Abuse History	No history of alcohol use (MAST score of 0)	No history of alcohol dependence (MAST score of 1-2)	Suggests alcohol dependence (MAST score of 5 or higher)
Depression	No depression (BDI-II score of 0)	Minimal depression (BDI-II score of 0-13)	Low to severe depression (BDI-II score of 14 or higher)
Anxiety	No anxiety (BAI score of 0)	Low level of anxiety (BAI score of 0-21)	Moderate to high level of anxiety (BAI score of 22 or higher)
Psychopathology	Low in neuroticism and high in conscientiousness (NEO-FFI)	Mid-range on neuroticism and conscientiousness (NEO-FFI)	High in neuroticism and low in conscientiousness (NEO-FFI)
Intelligence	High average and above intellectual functioning (WAIS-IV score of 110 and above)	Average intellectual functioning (WAIS-IV score of 90-109)	Borderline and lower intellectual functioning (WAIS-IV score of 89 or below)

Note: Where no psychometric instrument is noted in parentheses, the information is obtained by self-report with the understanding that degree of blindness and mental illness will be explored in greater depth by the ophthalmologist and psychiatrist, respectively.

In summary, the results from the Dobelle subjects interviews, and Chicago Lighthouse focus groups, have established our foundation for the volunteer selection and participation support protocol. There is no other vision prosthesis team in the world that matches our knowledge of the experiences of individuals who have previously been implanted with a vision prosthesis, and anticipated end-user needs. These have resulted in the development of the ICVP subject selection and inclusion criteria, above.

COMPLETION OF SOW TASK 5

Task 5. Constitute a team structure within a clinical setting for preparation of surgical implantation and human subject care.

The formation of our ICVP team is complete. We have added the Chicago Lighthouse for the Blind and Visually Impaired, the University of Texas, Dallas, and an Advisory Board. The team members and their roles are detailed in the table below:

Institution	*Team member - (*)Scientific Steering Group*	*Project Role*
Illinois Institute of Technology (IIT) Lead Institution **Project Management, Device and System Design, Psychology, Planning and Executing the Clinical Trial**	****Philip Troyk, Ph.D. (IIT PI)***	Project PI, Experimental design, WFMA Design/QA, IDE Preparation (with NAMSA)
	****Frank Lane, Ph.D.***	Psychology methods, Selection protocol, Recruitment
	Gayatri Kaskhedikar, M.S. (Ph.D. 08/2016)	ICVP testing at CLH: Threshold tests, Mapping
	Hillary Napier-Gondek, M.S. OTR/L	Occupational Assessment at CLH (IIT Consultant)
University of Chicago (UC) **Surgical Implanation, Subject Health, Seizure Filter Development, Visual Neuroscience, Experimental Planning**	****Vernon Towle, Ph.D. (UC PI)***	ICVP testing design, data analysis, image algorithms
	****David Frim, MD, Ph.D.***	Surgical implantation of ICVP
	Ben Roitberg, MD	Surgical implantation of ICVP
	Wim van Drongelen, Ph.D.	Defintion of seizure-resistant simulation filters
	Royce Lee, MD	Psychiatric exam of recipient pool
	Susan M. Ksiazek, MD	Ophthalmic and visual assessment
	Ted Karrison, Ph.D.	Biostatistician for data processing
	Naoum Issa, M.D., Ph.D.	Vision scientist; Epileptologist
	John Maunsell, Ph.D.	Advisor for higher-order percept neural coding
Johns Hopkins University (JHU) **Psychophysical Testing**	****Gislin Dagnelie, Ph.D. (JHU PI)***	Definition and oversight of ICVP testing at CLH
	James Deremeik, M.Ed., CLVT	Use of ICVP for wayfinding and daily living tasks
Chicago Lighthouse (CLH) **Services for Subjects, ICVP Testing Laboratory, OT/OM Training/Assessment**	****Janet Szlyk, Ph.D. (CLH PI)***	Experimental design/oversight at CLH
	Ana Williams Leffel, M.A.	Certified Orientation and Mobility Specialist
	Patricia Rodriguez	Patient Advocate
University of Texas, Dallas (UTD) **GLP testing & GMP-compliance Coordination**	****Stuart F. Cogan, Sc.D. (UTD PI)***	Materials conformance, electrodes, safe stimulation.
	Diana Easton,Ph.D.	Regulatory process oversight and assurance.
NAMSA **GLP Large Animal & ISO10993 Testing, IDE Submission Preparatory Consulting**	Contract Research Organization	CRO for GLP testing, IDE preparation, Project Monitoring (IIT Consultant)
MicroProbes for Life Science (MLS) GMP-compliant Manufacturing of WFMAs	****Martin Bak, B.S. (MLS PI)***	WFMA Fabrication and Delivery
	Nicolas Alba, Ph.D.	WFMA GMP-compliance
Sigenics, Inc **GMP-compliant Manufacturing of Electronic Components**	****Zhe Hu, Ph.D. (Sigenics PI)***	Telemetry Controller (TC) Design
	Glenn DeMichele, M.S.	GMP-compliant ASIC/Coil Testing, Delivery
ICVP Advisory Board	Richard Penn, MD	Professor, Dept. of Neurosurgery, Rush Medical School Adjunct Professor of Bioengineering, University of Illinois, Chicago
	Itzhak Fried, MD	Professor of Surgery/Neurosurgery, Director of Epilepsy Surgery, UCLA School of Medicine
	Timothy J. Denison, PhD	Sr. Director, Neuromodulation Core Technology, Medtronic, Inc, Adjunct Professor of Engineering, Brown University
	Marcia J. Scherer, Ph.D., MPH	Professor of Physical Medicine and Rehabilitation, University of Rochester
	Paul Mason, PhD	Vice President, RA/CA/QA, ImThera Medical, Inc.
	Richard Martinez	CEO Martinez Management

Our team has collaborated on the ICVP project for 15 years, and consists of non-clinical and clinical scientists/engineers, disease experts, regulatory experts, statisticians, experts in manufacture under Quality Systems and Design Controls, and other experts specific to cortical visual prostheses. In preparation for the clinical trial, our team has defined an overall device development plan ensuring that needed gaps have been clearly defined and can be addressed during the funding period to execute the research strategy. The above organizational chart clearly defines the team structure and relationships among the various components, as well as the governance and organizational structure of the leadership team. Our Scientific Steering Group is comprised of representatives from each of the partnering organizations, as indicated in bold font, above. The geographic separation between the institutions presents no significant barrier to team interaction. Physical team meeting will be held: preclinical phase (each 2 months); clinical phase (each 3 months). **1)**IIT, UC, and CLH are within 10 minutes driving distance from each other; **2)**Dr. Troyk has an academic appointment in Neurosurgery at UC, and in collaboration with several research programs, often spends 2-3 days/week at UC. **3)**Dr. Dagnelie has been directing Dr. Troyk's Ph.D. student, Ms. Kaskhedikar (for development of cortical mapping techniques), in residence in his lab at JHU for the past two years (cumulative 9 months), with regular joint IIT teleconferences. **4)**Dr. Troyk has made 6 trips to UTD (1.5 hour flight) in the past year coordinating WFMA testing in the UTD laboratories with Dr. Cogan. **5)**Dr. Cogan is a PhD thesis committee member of another of Dr. Troyk's students at IIT, interacting via web conferencing. **6)**Mr. Bak, of MLS, is in frequent communications with Dr. Troyk, visits the IIT laboratories relative to WFMA design and manufacturing, and Dr. Troyk has similarly visited MLS. **7)**Sigenics, Inc, is located on the IIT campus near Dr. Troyk's IIT laboratory, and has sophisticated video conferencing capabilities for weekly team meetings. **8)**Dr.

Lane's PhD student Melissa Bangle (Troyk) is regularly at the CLH as part of her internship program. **9)**Our team has numerous joint publications, spanning 15 years. Our Advisory Board has a diverse mix of expertise and experience: Dr. Penn was involved with the ICVP project when it was at NIH. Dr. Fried has essential expertise in epilepsy and seizures. Dr. Denison is a Medtronic Fellow, well-known in the Neural Interface community, and has prior experience in visual prostheses. Marcia Scherer has a prominent career in assistive technology psychology, Paul Mason has 25 years of experience in Class III implanted devices, and Rich Martinez is the father of two twin boys with blindness.

This team has all of the expertise needed for deployment of the ICVP in a clinical trial. The working relationships are intimate, with publications and conference presentations crossing disciplines.

In summary, the goals of Task 5 have been accomplished and the ICVP group is an unprecedented team of expert individuals who have working relationships that are active and unified towards the goal of the clinical trial.

COMPLETION OF SOW TASK 6

Task 6. Preparation and submission of an FDA IDE application for a human trial.

This is the culminating Task for the project work. In formulating the goal of submission of the IDE to the FDA we were somewhat naïve about the scope of what was required. Therefore while we have not submitted the IDE, we have had three pre-IDE teleconferences with the FDA, and we have identified the following issues that we will address during the pre-clinical phase (2 years) of our clinical trial project, as proposed to the NIH.

Since April 2015, we have had three teleconferences with the FDA to discuss our plans for the ICVP clinical trial attended by: Drs. Angelo Green (acting branch chief), Tieuvi Nguyen, Erin Keegan, and Bernie Lepri. We obtained the following guidance about our ICVP clinical trial plans:

1) Our Early Feasbility Study/First in Human (EFS/FIH) IDE submission will be reviewed in the Division of Ophthalmic and Ear, Nose and Throat Devices (DOED), Contact Lenses and Retinal Devices (CLRD) Branch.

2) The recommended animal for the GLP Large Animal Studies is Dog, rather than Sheep. This is confirmed by NAMSA our partnering contract research organization.

3) Use of multiple Pre-sub meetings is crucial to FDA IDE evaluation and approval – we are planning for 3 Pre-sub meetings. Use of the Pre-sub meetings by applicants has reduced the average IDE approval time from 442 days in 2011, to 30 days in 2015 – we are allowing 6 months for IDE approval.

4) In FY2015, 73.5% of IDEs were approved within two submission cycles, and 69% of EFS/FIH IDEs were approved (link).

5) The main criteria for approval of an EFS/FIH is safety. It is expected that efficacy will be determined during the trial. We will need to perform ISO10993 toxicology tests and GLP large animal tests prior to IDE submission.

6) GLP large animal safety studies need to be in occipital cortex. We will perform our GLP studies in Dog occipital lobe using same density of implants planned for humans.

7) In EFS/FIH trials, study informed changes in device configurations are not unexpected. Potential system variations during the trial must tested in the animal studies. We will test electrode length variations in our GLP studies at NAMSA to prepare for variations during the trial.

8) Our plans for testing and conformance of the polymers used in the WFMA sound reasonable at this Pre-sub stage.

9) Complete schematics and software code submission should be made with the IDE submission. We have a documentation process in place at both MLS and Sigenics that is GMP-compliant and the required documents will be easily collated with assistance from NAMSA.

10) The Device Evaluation Strategy Table is a key document for Pre-sub discussion. Our Table will be ready for FDA Pre-sub discussion at the start of the project for the first Pre-sub meeting in month 1.

11) Owing to the small size of the WFMA, and the total device surface area required for ISO10993 testing, fabricating a physically larger facsimile versions of the WFMA is a reasonable approach – frequently occurs. 12) Some EFS/FIH applications have used 90-day rather than 180-day GLP large animal testing. We plan to use 180-day testing. Summary: Based upon these teleconferences, there is a high-likelihood that ICVP team can obtain an approved IDE for the desired ICVP clinical trial within a 2-year clinical phase.

An important outcome of the TATRC-funded project is the formulation of the following preclinical plan that is part of the IDE submission process. The cost of implementing this plan far exceeds the funds that were available under the TATRC project, however, the preparatory work and the formulation of the plan are significant outcomes of our completion of Task 6:

To efficiently conduct ICVP development under Design Controls and perform the needed GLP safety testing, we have engaged a contract research organization (CRO), **NAMSA** (https://www.namsa.com/), to conduct GLP testing and to assist in developing and executing our strategy for obtaining FDA approval for the early feasibility study. Dr. Easton at UTD will oversee NAMSA activities. We have chosen this approach because of NAMSA's extensive prior experience with pre-clinical testing of brain implants for IDE applications. Our team has established a flowchart of testing and support functions to be provided by NAMSA.

ICVP specifications will be formulated under Design Controls in accordance with 21 CFR part 820.30. The ICVP manufacturers, MicroProbes and Sigenics currently meet Quality System regulations (GMP). The Design Controls process for the ICVP, includes establishing and maintaining plans that describe design and development activities and also defining responsibility for implementation. All of these will be ready for project use on the UG3 start date. In M1-2, risk management and risk mitigation measures (hardware, software, system and labeling as part of the informed consent) will be identified and implemented in accordance with applicable sections of ISO 14971 and ISO 62304 and integrated with the Device Evaluation Strategy (DES). The DES will describe the ICVP and attributes necessary to achieve visual percepts, including, for each attribute, a risk/benefit assessment identifying significant safety concerns, potential failure modes and design characteristics, required testing, manufacturing controls, and clinical study strategies required to mitigate the failure modes. The DES, including a performance related attribute DES Table, will be incorporated into the M1 pre-sub meeting with the FDA, and updated based on feedback received. Records of all activities will be maintained as detailed in CFR 812.140 for Significant Risk Device Studies.

ICVP acceptance criteria and compliance with specifications and FDA requirements for EFS: Conformance of the ICVP system to the specifications will be determined by testing against acceptance criteria. These criteria will be for all lab bench, laboratory and animal test results included in the EFS-IDE submission to the FDA.

A **manufacturing plan** will be developed to define the procedures and actions necessary to control the manufacture of the device to meet specified design requirements, e.g. inspection and test criteria, and plan for mitigations of potential failure modes that could result from uncontrolled manufacturing processes. This plan will be developed together with and include the collaborators and facilities involved in the ICVP manufacture.

A **test plan** will be developed, including prior completed testing, to mitigate failure that might occur with the device design and intended use. The plan will identify and allow for the collection of data from which device safety to support the EFS IDE application can be obtained. Preclinical testing will be performed on both the device level and system level, e.g. implant and controller. In accordance with FDA IDE guidance, the test plan will include detailed purpose, sample size and statistical methods, test methodology (including the recognized standard where available) and the acceptance criteria with rationale for each test. Testing will be performed to existing, FDA recognized standards and where available, in certified (GLP) facilities in order to assure the quality and integrity of the test data to mitigate risk and support the IDE application.

A **clinical trial outline** will be developed, in accordance with FDA Pre-sub guidance that will include target patient population, patient selection criteria, study endpoints, length and type of follow-up.

The pre-sub process provides FDA's targeted feedback on planned testing and trial design prior to the IDE submission. Our team has already used this process, informally, via three teleconferences with the FDA. Pre-sub documentation will be ready at the start of the preclinical phase and will include background history, a device description, engineering drawings, explanation of the materials used, a discussion of the mechanism of action, manufacturing plans, how the device will be used clinically, and the proposed intended use. The Pre-sub packet will also include the Test plan, planned bench and animal testing, the rationale for the proposed test strategy based on the risk analysis and device evaluation strategy; and the Clinical outline. Feedback received, and/or issues raised as part of the pre-sub meeting will be incorporated, addressed or resolved prior to subsequent Pre-sub meeting and the submission of the subsequent IDE application. We anticipate up to three Pre-sub FDA meetings in order to fully exploit the advantages of the Pre-sub process. Shortening the IDE approval time is directly related to applicants' effective use of the Pre-sub process.

The sterilization process will be validated by a certified test facility according to the FDA recognized consensus revision of ISO 11135. Integrated with the sterilization testing will be applicable package testing to ensure the sterile barrier is maintained through point of us.

NAMSA will provide guidance in the conduct and preparation of the preclinical studies for IDE submission and conduct all GLP pre-clinical biocompatibility and large-animal safety studies. The anticipated scope and schedule of

these studies has been developed in collaboration with NASMA. Biocompatibility studies will be conducted using devices conforming to the validated GMP fabrication process. When necessary to meet sample size requirements, geometrically scaled-up versions of the devices fabricated in accordance with the validated fabrication process will be used. All study samples will be packaged and sterilized in accordance with the validated sterilization process. Suitability for long-term implantation will be assessed in accordance with the FDA-recognized consensus revision of ISO 10993-1, and include cytotoxicity, ISO maximization sensitization, ISO intracutaneous by extract, ISO systemic toxicity by extract (rat), systemic toxicity by implant (rat: 13 and 26 week), pyrogenicity, subchronic toxicity, and genotoxicity. The implantable components may be evaluated for biocompatibility in terms of carcinogenicity and chronic toxicity, without the need for further testing per ISO 10993-1 and FDA G95-1 guidelines, depending upon the results of the material characterization testing.

Following consultation with NAMSA and the FDA, dog has been chosen as the species for the large-animal safety study. The alternative is sheep. While sheep may be regarded as typically for large animal testing in brain implant studies, dog is preferable for the ICVP project because the animals exhibit fewer baseline morbidity or mortality events than sheep, are amenable to detailed neurobehavioral evaluation, the occipital lobe brain surface area is comparable, and their skulls are thinner and more human-like than sheep. Dog has also been used previously by NAMSA for large-animal safety studies of brain implants to support of IDE applications of other sponsors. Furthermore, the dog model has already been suggested to our team during our prior FDA teleconferences. Currently, GLP studies with termination intervals of 4, 12 and 26 weeks have been planned and budgeted. The scope of the study will be a topic in the M1 pre-sub meeting with the FDA and be reduced depending on the outcome of that meeting.

A four, 12, and 26 week GLP study of WFMA implants in dog will be conducted. The study will involve an anticipated 28 purpose-bred hounds. WFMA devices will be implanted in the occipital cortex at an equivalent or larger device/brain size ratio than anticipated for the human, and will likely use 4 devices within a 1x2 cm durotomy, considering the size limitations of the dog brain. There will be four animals, each, in the implant and control groups for each time point (4x2x3=24 minimum). Outcomes will include: daily and detailed (weekly) health observations; gross pathology of the brain and histology including H&E, Fluoro-Jade B, and GFAP. Evaluation will be conducted by a qualified pathologist (draft annex D of ISO 10993 Part 60) and include: inflammatory response, necrosis, neovascularization, fibrosis, astrocytosis, adhesions, mineralization, foreign body reaction and CSF leakage. WFMA implants will be assessed for degradation and then returned to MLS/Sigenics for further evaluation.

Electromagnetic interference and electromagnetic compatibility testing will be completed by a certified test lab in accordance with requirements set forth in the FDA recognized consensus revisions of IEC 60601-1-2 and EN 300 330-1 for intentional and unintentional radiators. Basic safety and essential performance for medical electrical equipment and active implantable systems will also be completed in a certified test lab in accordance with the FDA recognized consensus revisions of IEC 60601-1.

In summary, the goals for Task 6 have been accomplished. Although the full scope, and cost, of these were underestimated as part of the TATRC proposal, the development of the pre-IDE plan, and the firm definition of the IDE submission costs was the primary goal of Task 6. Our team is now positioned to begin the IDE submission in support of the clinical trial. That plan for the clinical trial has been submitted to NIH in response to a pre/clinical trial project under the BRAIN initiative.

KEY RESEARCH ACCOMPLISHMENTS

- Maturation and demonstration of the robustness, reliability, and readiness of the ICVP technology for the human clinical trial.
- Establishment of novel and advanced psychophysical testing methods
- Implementation of a portable ICVP image processing system
- Establishment of psychological testing and volunteer selection protocols based upon experiences of prior visual prosthesis recipients and focus groups of potential volunteers. Definition of the subject inclusion/exclusion criteria.

- Establishment of the multi-disciplinary ICVP team, with on-going and active participation by all team members.

- Defined plan for submission of IDE to the FDA for an ICVP clinical trial.

REPORTABLE OUTCOMES

Papers/Presentations during the post-award notification/pre-award start date period

1. Bredeson, S.D.; Troyk, P.R., "Device for the implantation of neural electrode arrays," Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE , vol., no., pp.434,437, 26-30 Aug. 2014
2. Bredeson, SD; PR Troyk, S Suh, M Bak. "Identification and quantification of electrical leakage pathways in floating microelectrode arrays," 35th Annual International Conference of the IEEE EMBS, pp. 1542-1545, Jul 2013. Link
3. Bredeson, SD; PR Troyk, S Suh, M Bak. "Investigation of long-term electrical degradation in neural recording and stimulation microelectrode arrays," 6th International IEEE EMBS Conference on Neural Engineering, pp. 621-624, Nov 2013. Link
4. Bredeson, SD; PR Troyk. "Device for the implantation of neural electrode arrays," 36th Annual International Conference of the IEEE EMBS, pp. 434-437, Aug 2014. Link
5. Detlefsen, DE; Z Hu, PR Troyk. "A LabVIEW based experiment system for the efficient collection and analysis of cyclic voltametry and electrode charge capacity measurements," 28th Annual International Conference of the IEEE EMBS, pp. 2998-3001, Sep 2006. Link
6. F. J. Lane, M. Huyck, P.R. Troyk, K. Schug; "Responses of potential users to the intracortical visual prosthesis: final themes from the analysis of focus group data" Disability and Rehabilitation: Assistive Technology, Vol. 7, No. 4 , Pages 304-313, July 2012
7. Frank J. Lane, Margaret H. Huyck, and Philip R. Troyk, "The Experiences Of Recipients Of A Cortical Visual Prosthesis: A Preliminary Analysis Of Nine Participants Expressed Motivation, Decision-making Process, Risks, And Functional Use Of Phosphenes," ARVO Meeting Abstracts March 26, 2012 53:5553, 2012
8. Frank John Lane, Kristian Nitsch, Margaret Huyck, Philip Troyk, Ken Schug, "Perspectives of optic nerve prostheses," Disability and Rehabilitation: Assistive Technology : 1–9. (doi:10.3109/17483107.2014.961178) Posted online on 26 Nov 2014.
9. G.Kaskhedikar, P.R. Troyk, "Identifying the challenges in the development of an effective intracortical visual prosthesis system: Utilization of patient feedback" Proceedings 7th World Congress on Visual Prostheses: Eye and the Chip" 2012 (Poster presentation)
10. Gayatri P. Kaskhedikar, Zhe Hu, Gislin Dagnelie and Philip R.Troyk, "Proposed Intracortical Vision Prosthesis System for Phosphene Mapping and Psychophysical Studies," 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 880-882
11. H. Zhe, P. Troyk, G. DeMichele, K. Kayvani, S. Suh, "Intrinsic Activation of Iridium Electrodes over a Wireless Link" 34th Annual International Conference of the IEEE EMBS pp. 2788-2791, 2012
12. Hu, Z; PR Troyk, DE Detlefsen. "Analysis of capacitive coupling within microelectrode array," 28th Annual International Conference of the IEEE EMBS, pp. 3365-3368, Sep 2006. Link
13. Hu, Z; PR Troyk, SF Cogan, M Bak, D Margoliash. "In-vivo evaluation of AIROF microelectrodes for an Intracortical Visual Prosthesis," Proceedings of the 5th World Congress on Visual Prostheses: Eye and the Chip, 2008. Link
14. Hu, Z; PR Troyk, SF Cogan. "A 96-channel neural stimulation system for driving AIROF microelectrodes," 26th Annual International Conference of the IEEE EMBS, pp. 4244-4247, Sep 2004. Link
15. Hu, Z; PR Troyk, SF Cogan. "An automatic monitor system for AIROF microelectrodes," 27th Annual International Conference of the IEEE EMBS, pp. 7386-7388, Jan 2006. Link
16. Hu, Z; PR Troyk, SF Cogan. "Comprehensive cyclic voltammetry characterization of AIROF microelectrodes," 27th Annual International Conference of the IEEE EMBS, pp. 5246-5249, Jan 2006. Link

17. Hu, Z; PR Troyk, TP Brawn, D Margoliash, SF Cogan. "In vitro and in vivo charge capacity of AIROF microelectrodes," 28th Annual International Conference of the IEEE EMBS, pp. 886-889, Sep 2006. Link
18. Hu, Z; PR Troyk, TP Brawn, D Margoliash, SF Cogan. "Polarization of AIROF microelectrodes in charge delivery," 3rd International IEEE/EMBS Conference on Neural Engineering, pp. 134-136, May 2007. Link
19. Kaskhedikar GP; Zhe Hu, G Dagnelie, PR Troyk. "Proposed Intracortical vision prosthesis system for phosphene mapping and psychophysical studies," 6th International IEEE EMBS Conference on Neural Engineering, pp. 880-882, Nov 2013. Link
20. Kim, T; Z Hu, M Bak. "Active floating micro electrode arrays (AFMA)," 28th Annual International Conference of the IEEE EMBS, pp. 2807-2810, Sep 2006. Link
21. Margaret H. Huyck, Frank Lane, Kenneth Schug, and Philip Troyk, "Looking Forward by Looking Back: Comparing Anticipations with Actual Experiences with a Visual Cortical Implant Prosthesis," ARVO Meeting Abstracts March 26, 2012 53:5554, 2012
22. Philip R. Troyk,Sungjae Suh, Zhe Hu, Kevin Kayvani, Glenn DeMichele, and Douglas Kerns, "Assessment Of Technology For An Intracortical Visual Prosthesis" ARVO Meeting Abstracts March 26, 2012 53:5552, 2012
23. Rush, A; PR Troyk. "A Power and Data Link for a Wireless Implanted Neural Recording System," IEEE Transactions on Biomedical Engineering, vol. 59, no. 11, pp. 3255-3262, Nov 2012. Link
24. Rush, A; PR Troyk. "Dual inductive link coil design for a neural recording system," 33rd Annual International Conference of the IEEE EMBS, pp. 6397-6400, Aug 2011. Link
25. Rush, A; PR Troyk. "Electronic performance of a dual inductive link for a wireless neural recording implant," 33rd Annual International Conference of the IEEE EMBS, pp. 6348-6351, Aug 2011. Link
26. Rush, A; PR Troyk. "Power and Data for a Wireless Implanted Neural Recording System," 5th International IEEE EMBS Conference on Neural Engineering, pp. 507-510, Apr 2011. Link
27. Rush, A; S Suh, PR Troyk. "An Inductive Link for an Intracortical Visual Prosthesis," 5th International IEEE EMBS Conference on Neural Engineering, pp. 503-506, Apr 2011. Link
28. S. Bredeson,P. Troyk, S Suh, M. Bak. "Identification and Quantification of Electrical Leakage Pathways in Floating Microelectrode Arrays." 35th Annual International Conference of the IEEE EMBS pp. 1542 – 1545 2013
29. Samuel D. Bredeson, Philip R. Troyk, Sungjae Suh, and M. Bak, "Investigation of Long-Term Electrical Degradation in Neural Recording and Stimulation Microelectrode Arrays," 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 621 -624
30. Srivastava, NR; PR Troyk, D Bradley. "FPGA based visual prosthesis device for testing visual perception on non-human primates," IEEE International Conference on Electro/Information Technology, pp. 21-25, May 2007. Link
31. Srivastava, NR; PR Troyk, G Dagnelie, D Bradley. "Test setup for supporting human implantation of intracortical visual prosthesis device," 3rd International IEEE/EMBS Conference on Neural Engineering, pp. 442-445, May 2007. Link
32. Srivastava, NR; PR Troyk, G Dagnelie. "Detection, eye-hand coordination and virtual mobility performance in simulated vision for a cortical visual prosthesis device," Journal of Neural Engineering, vol. 6, no. 3, Jun 2009. Link
33. Srivastava, NR; PR Troyk, SF Cogan. "A laboratory testing and driving system for AIROF microelectrodes," 26th Annual International Conference of the IEEE EMBS, pp. 4271-4274, Sep 2004. Link
34. Srivastava, NR; PR Troyk, VL Towle, D Curry, E Schmidt, C Kufta, G Dagnelie. "Estimating phosphene maps for psychophysical experiments used in testing a cortical visual prosthesis device," 3rd International IEEE/EMBS Conference on Neural Engineering, pp. 130-133, May 2007. Link
35. Srivastava, NR; PR Troyk. "A proposed intracortical visual prosthesis image processing system," 27th Annual International Conference of the IEEE EMBS, pp. 5264-5267, Jan 2006. Link
36. Srivastava, NR; PR Troyk. "Some solutions to technical hurdles for developing a practical intracortical visual prosthesis device," 28th Annual International Conference of the IEEE EMBS, pp. 2936-2939, Sep 2006. Link
37. Srivastava, NR; PR Troyk. "Testing and monitoring system for a first generation intracortical visual prosthesis device using Java, Labview and VGA/NTSC output," IEEE International Conference on Electro/Information Technology, pp. 521-526, May 2007. Link

38. Suh, S; PR Troyk, Z Hu. "Accelerated-stress reliability evaluation for an encapsulated wireless cortical stimulator," 36th Annual International Conference of the IEEE EMBS, pp. 442-445, Aug 2014. Link
39. Sungjae Suh; Troyk, P.R.; Zhe Hu, "Accelerated-stress reliability evaluation for an encapsulated wireless cortical stimulator," Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE , vol., no., pp.442,445, 26-30 Aug. 2014
40. Troyk, P.; Hu, Z., "Simplified Design Equations for Class-E Neural Prosthesis Transmitters," IEEE Transactions on Biomedical Engineering, vol.60, no.5, pp.1414-1421, May 2013
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42. Troyk, PR; D Bradley, M Bak, SF Cogan, D Curry, Z Hu, C Kufta, M Lusignan, D McCreery, E Schmidt, VL Towle. "An Intracortical V1 Visual Prosthesis: Balancing Functional, Surgical, and Technological Considerations," ARVO Meeting Abstracts, May 2007. Link
43. Troyk, PR; D Bradley, M Bak, SF Cogan, R Erickson, Z Hu, C Kufta, D McCreery, E Schmidt, S Sung, VL Towle. "Intracortical visual prosthesis research - approach and progress," 27th Annual International Conference of the IEEE EMBS, pp. 7376-7379, Jan 2006. Link
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46. Troyk, PR; NR Srivastava, Z Hu, M Bak, SF Cogan, C Kufta, D McCreery, E Schmidt, VL Towle. "Towards Implantation of the Intracortical Visual Prosthesis: Combining Technology, Pyschophysics, and Surgical Considerations," Proceedings of the 38th NIH Neural Prosthesis Workshop, NINDS, 2007. Link
47. Troyk, PR; Z Hu, SF Cogan. "Assessing polarization of AIROF microelectrodes," 29th Annual International Conference of the IEEE EMBS, pp. 1726-1729, Aug 2007. Link
48. Z. Hu, P. Troyk, G. DeMichele, D. Kerns, M. Bak, "A laboratory instrument for characterizing multiple microelectrodes, "35th Annual International Conference of the IEEE EMBS pp. 1558 – 1561, 2013

Presentations during the post-award notification/pre-award start date period

49. P. Troyk, F. Lane, 17th Annual Conference of the International Functional Electrical Stimulation Society, Banff, Alberta, CA, "Experiences of Recipients of Cortical Visual Prosthesis Implants - Lessons for all Neural Prostheses," September 12, 2012 (invited presentation)
50. F. Lane, P. Troyk, "Intracortical Visual Prosthesis: Assessing Readiness for a Clinical Trial," 7th World Congress on Visual Prostheses, Detroit MI, September 11, 2012. (invited presentation)
51. Philip R. Troyk, "Intracortical Visual Prosthesis – Assessing Readiness for a Clinical Trial" Proceedings 7th World Congress on Visual Prostheses, Congress on Visual Prostheses: Eye and the Chip, Detroit MI, September 12, 2013
52. Philip R Troyk "Intracortical Visual Prosthesis: Status of the Clinical Trial Preparations" Proceedings 8th World Congress on Visual Prostheses, Congress on Visual Prostheses: Eye and the Chip, Detroit MI, September 28 - 30, 2014
53. F. Lane "Analysis and results of interviews of fourteen recipients of a cortical vision implant," Proceedings 8th World Congress on Visual Prostheses, Congress on Visual Prostheses: Eye and the Chip, Detroit MI, September 28 - 30, 2014

CONCLUSION

Progress towards the clinical trial deployment of the ICVP made possible through the work performed under this project has been excellent. Examination of the accomplishments, as detailed above, demonstrate that essential steps have been made towards the goal of this project: preparation for the clinical trial.

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